8-Methoxypsoralen

A Short Review and Comment

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• **8-Methoxypsoralen is a purified extract of the root *ammi majus lynn*, which was used in a crude form for centuries in the Middle East in the treatment of various skin diseases. In recent years it has been found that the purified extract, when taken internally, increases all skin responses to sunlight, including tanning. When too much drug is taken or when the patient is exposed to sunlight too long, the preliminary erythema may be painful, and blistering may occur. In some patients with vitiligo, islands of pigmentation appear around the hair follicles when the drug is taken, and in favorable cases these islands may coalesce to form continuous areas of pigmented skin. The drug has been found nontoxic, but successful treatment of vitiligo takes place in only a small proportion of patients.**

Promiscuous use of the drug for cosmetic tanning is to be deplored. The constant irritation of the skin due to the increased action of sunlight when the drug is used may possibly increase the incidence of sun-induced skin cancers.

A topical preparation is available, which, when used with great care, may help to repigment small areas of vitiligo.

IN ANCIENT TIMES, many skin diseases were regarded as forms of leprosy. Because leukodermia is often seen in Hansen's disease, it is probable that fear of being shunned as lepers prompted sufferers from vitiligo to use oral and topical preparations of the plant *Ammi majus Linn*, which grows along the Nile. The crude preparation taken by mouth was reputed to cause many serious side effects, the most significant being liver damage. In 1947, two Egyptian biochemists, Fahmy and Abu-Shady,[4] isolated the most active principles from the plant and found them to be furocoumarins—highly photosensitizing compounds. One of these, 8-methoxypsoralen (8-MOP) is the main constituent of the extract.

Until the discovery of 8-MOP no satisfactory treatment for vitiligo existed. The new preparation was eagerly investigated and within a short time a plethora of enthusiastic papers was forthcoming. Work has been almost continuous and the purpose of this short paper is to summarize the more clinical aspects of these efforts. The comments will be my own and may not entirely agree with those of other investigators.

There is no doubt that 8-MOP in some way increases sun tanning. In the normal skin of dark persons a rich tan is produced, and with care moderate tanning will take place in the fair skinned and even in redheads. In vitiligo, as is well known, pigment production upon use of this drug commences in follicular islands (Figure 1), and in favorable cases these islands coalesce to form unbroken areas of pigment. Unfortunately, the treatment is tedious and often frustrating. While in some patients new pigment formation becomes obvious in as short a time as two weeks, in most cases several weeks and even months of therapy is necessary before repigmentation commences. Moreover, in many patients follicular islands may appear but never join with one another; some persons may completely repigment in certain areas and not produce any new melanin in others; and finally, even

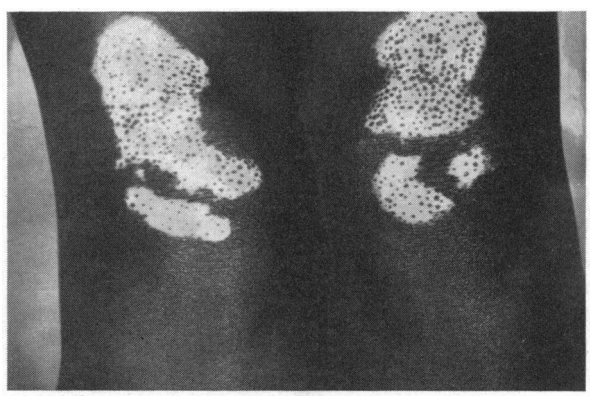

Figure 1.—Good follicular response about the knees to 8-MOP.

in successful cases the new pigmentation may fade after treatment is stopped. In a recent paper Levai[5] commented on the sites in which treatment is more likely to be successful. Taking complete repigmentation as the only criterion (for obviously partial follicular repigmentation is cosmetically as undesirable as vitiligo) the treatment has been effective in

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perhaps 30 per cent of cases in which I have used it. Even this relatively small success is an advance.

In an effort to save the unfortunate majority of patients expense and inconvenience by attempting to forecast success or failure at the first interview, certain criteria may be noted. Speaking generally, the older the vitiligo the worse the prognosis. Many patients will show follicular islands of melanin at the first examination, and these are presumably of favorable significance. A theory that is deserving of more attention is that put forward by Pegum.[7] He noted that the work of Billingham and Medawar[2] established that in man and certain animals two distinct melanocyte systems exist, one in the basal layer and one in the hair apparatus. These are anatomically distinct because the melanocytes of the basal layer surround the neck of the hair follicle but do not run down to the hair bulb, where another group of melanocytes is found. Physiologically, they are demonstrably distinct because one may find dark hairs in white skin in man, and red hairs in black skin in guinea pigs; and using cell suspensions and a microcannular technique, black melanocytes can be introduced into red or white hair follicles and result in the growth of black hairs. Billingham and Medawar removed areas of skin in Thiersch-graft thickness from guinea pigs, thus removing the melanocytes in the basal layer, and found that skin would regenerate entirely from the intact hair bulbs, with the pigment cells derived from the hair follicles also.

Using this work as a guide, Pegum attempted to treat vitiligo by removing epidermis in several ways. He took a Thiersch-graft thickness in two patients, blistered other vitiligo areas with carbon dioxide snow, and with cantharidin, and in other ways attempted to get rid of the inactive basal melanocytes. In several of these experiments, repigmentation from the hair follicles resulted. Correlating this work with the reports of follicular repigmentation taking place with 8-MOP therapy, he suggested that in an area of vitiligo where the hairs are pigmented a good result with 8-MOP may be anticipated. Conversely, if the hairs are white and depigmented (Figure 2) the prognosis is poor.

Much has been written regarding the possible toxic effects of psoralen. Transient changes in liver profile studies have been reported but in some of these there were no pretreatment studies.[3] In the others the abnormalities have quickly reversed following termination of treatment. Two cases of jaundice proved to be of viral origin. There have been four reports of development of light sensitivity in previously normal persons.[9] Five patients noted muscular incoordination which disappeared when they no longer took the drug.[10] No report of serious toxicity has yet been forthcoming in a collection of literature which must surely cover many hundreds of cases.

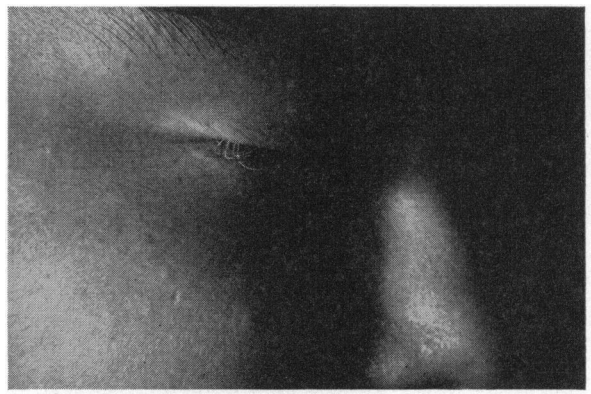

Figure 2.—Vitiligo of eyelid showing depigmented lashes. There was no response to treatment with 8-MOP.

Tucker[11] recently thoroughly evaluated this aspect of psoralen therapy in an excellent review. No drug has been more maligned than 8-MOP on this score and none more thoroughly investigated and exonerated. To my mind, the danger in 8-MOP therapy consists in the hazards associated with sunburning. Even when the skin is tanned, any intensive period of sun exposure after taking the drug produces erythema beneath the tan, and a sensation of burning. Although it has been suggested that 8-MOP could be used to produce a protective tan in patients prone to form basal cell carcinomas, it has been my feeling that it will potentiate the formation of skin cancer—as it does all the other effects of sunlight. Thus, it is interesting to note that Stegmaier[8] reported the case of a 36-year-old male with no previous history of skin cancer who spent two weeks in the Colorado mountains while taking 8-MOP and who developed a basal cell carcinoma of the skin two months later.

It was originally assumed that the tanning action of the psoralens (see Figures 3 and 4) was due to increased melanogenesis and that the resultant heavy pigmentation afforded the sun-protection. A problem was to explain the protection claimed by some albino patients. Here we felt that the shielding must have been due to increased thickening of the skin, as suggested by European workers, notably Miescher.[6] This theory was not satisfactorily demonstrated until recently, when Becker[1] and later Zimmerman[12] produced experimental thickening of the skin following the ingestion of 8-MOP and ultraviolet irradiation. This thickening seems to be due partly to the formation of a stratum lucidum and partly to a lessening of shedding of the stratum corneum due to an increased cohesion of squamous cells. Melanin granules accumulate in the thickened

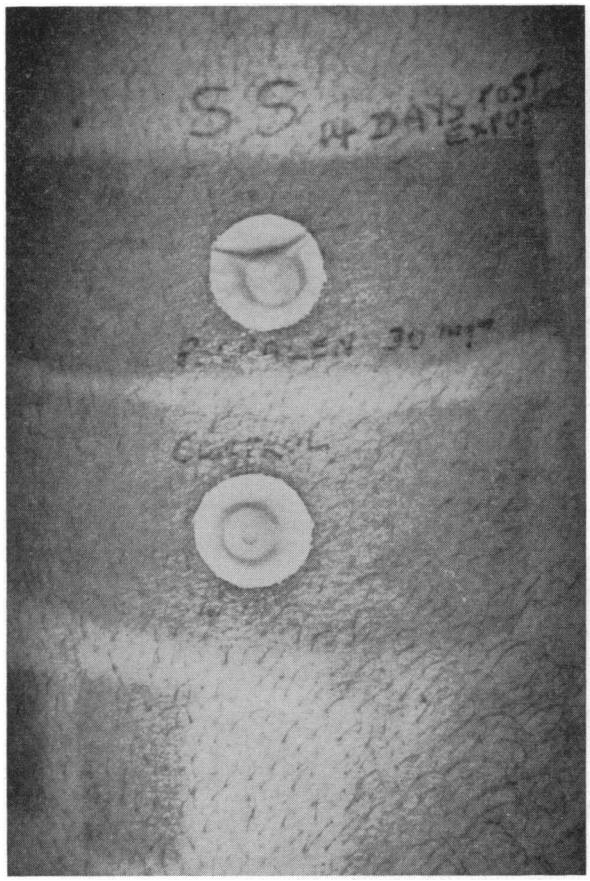

Figure 3.—Increased tanning following single one-hour exposure to sunlight after administration of 30 mg. of psoralen. Lower rectangle is control site.

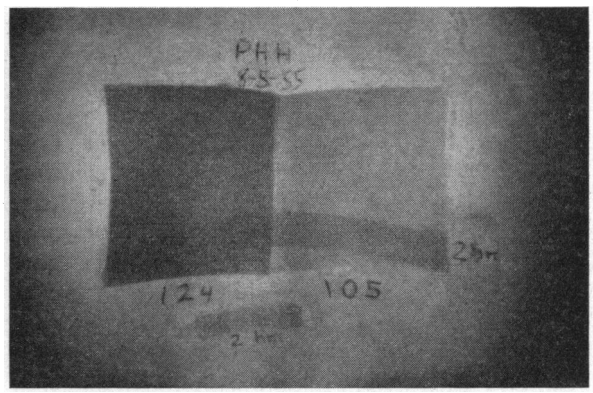

Figure 4.—Remarkable tanning effect of 8-MOP is demonstrated by this experiment in which the squares 124 and 105 were separately exposed to sunlight on alternate days. Square 124 was exposed following ingestion of 8-MOP, and 105 was control square.

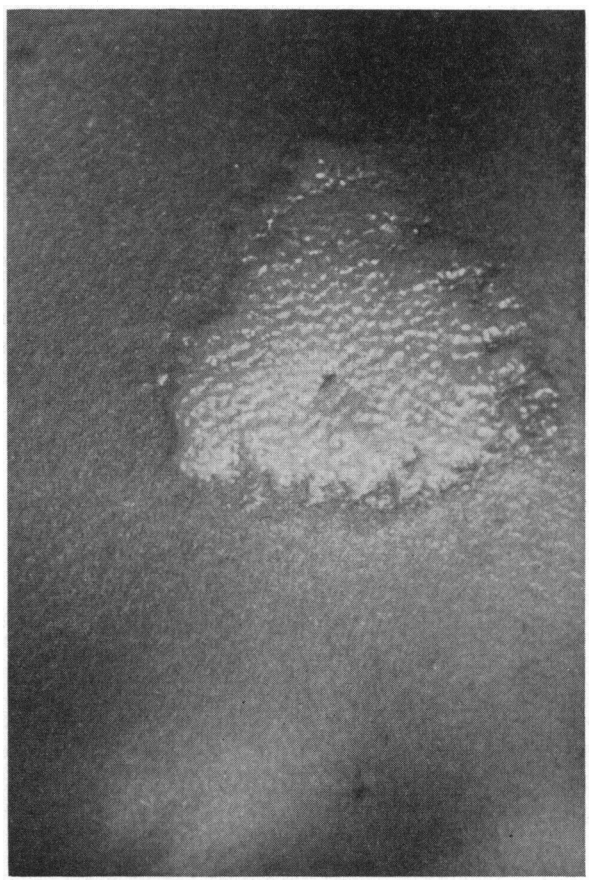

Figure 5.—Blistering following topical application of 8-MOP and excessive sun exposure.

stratum corneum and thus it darkens. A coincidental specific effect on melanogenesis has not been ruled out.

When treating a patient with vitiligo the problems associated with 8-MOP should be emphasized. The patient should be warned both as to length of treatment and the limited chances of success. It is my practice to stress that at first the vitiligo will be more obvious and indeed other patches of vitiligo may become apparent as the normal skin acquires the characteristic tan. The historical hazards of the treatment should be discussed, and a bromsulphthalein liver test should be carried out before treatment and periodically during therapy. The treatment should be commenced early in the summer to allow maximum time for repigmentation to occur. I have found that even in Southern California the sunlight is not strong enough to produce a good result in winter (even in the absence of smog) and that artificial ultraviolet light is not a good substitute for natural sunlight.

Finally, the patient is given thorough instruction regarding taking the drug. Twenty milligrams is the standard dose and should be exceeded rarely. Nausea, flatulence, burning in the throat and water brash are not uncommon and may sometimes be avoided by taking the capsules with a cookie and some milk. Sun exposure should be cautious and increased gradually; and in order to avoid medico-legal com-

plications detailed precautions regarding graduated sunbathing time are written on each prescription.

The topical preparation is potent and difficult to remove completely. Sloppy attempts at removal may wash some of the preparation onto surrounding skin and produce extensive burning after the next sun exposure (Figure 5). However, it may be used with caution on small areas of vitiligo.

Many physicians are afraid of using 8-MOP. In this regard it may be pointed out that there are many widely used drugs with dangerous potentialities. Penicillin is a good example. We do not forbid cigarettes because they may produce a carcinoma of the bronchus. Should we then condemn the psoralens because they may one day potentiate a relatively harmless skin cancer? The furocoumarins are abundant in many fruits and vegetables. An average celery stalk may contain over 1 milligram of psoralens. Used with understanding, 8-MOP has a place in the practice of dermatology.

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CORRECTION—3,178 gm., not 2,178

A TYPOGRAPHICAL ERROR that changed the purport of the sentence in which it appeared was made in the article "Pulmonary Hyaline Membrane Disease—The Obstetrician's Point of View," by Edward B. Cantor, M.D., which appeared in the January, 1960, issue of this journal.

On page 8, column 2, line 22 the weight of the infant was printed as 2,178 gm. It should have been 3,178 gm.